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October 29, 1999

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN'S PETITION

The undersigned submits this petition pursuant to 21 CFR 314.93 to request that the Commissioner of Food and Drug permit the filing of an Abbreviated New Drug Application for a drug that has the same active ingredient and dosage form listed in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", current Internet edition, but differs in its dosage strength (total quantity of active ingredient in the package).

A. Action requested

By this petition we hereby request the Agency to permit the filing of an Abbreviated New Drug Application for a Sterile Cefazolin Sodium, USP, pharmacy bulk package in 100-gram and 300-gram dosage strengths packaged in a plastic bag contained within a foil outer wrap. This drug differs from the listed drug, Eli Lilly and Company, Kefzol® (Sterile Cefazolin Sodium) 20 g Pharmacy Bulk Vials, in its total dosage strength but not the dosage amount recommended for administration to the patient.

B. Statement of grounds

In accordance with section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, a petition may be filed with the Agency seeking permission to file an Abbreviated New Drug Application for a new drug which differs from a "listed" drug in dosage strength. The Act stipulates that such a petition must be approved by the Agency unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product,

The reference listed drug product, Lilly's Kefzol® (Sterile Cefazolin Sodium) 20 g Pharmacy Bulk Vial, is identified in the Prescription Drug Product List of the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations"

99P-4870

CP 1

(Orange Book) as supplied in the current version of the CDER Internet home page. (A print out of this listing by active ingredient is provided in Attachment A.)

Our client proposes to develop a pharmacy bulk package of Sterile Cefazolin Sodium, USP, in 100g and 300g dosage strengths packaged in plastic bags themselves contained within a foil outer wrap. The inner (product) bag is provided with an injection port to allow aseptic constitution of the solution and transfer into dispensing units. The same formulation and route of administration as the listed drug pharmacy bulk pack are proposed, i.e., Sterile Cefatolin Sodium, USP, for intravenous injection after reconstitution with the specified diluent. The proposed product will be administered at the same dosage recommendations as the listed drug and is expected to have the same therapeutic effect when administered for use as indicated in the product labeling. The labeling for the listed drug, Eli Lilly and Company, Kefzol® (Sterile Cefazolin Sodium) Pharmacy Bulk Vial, is included in attachment B. The labeling for the proposed product is expected to be substantially the same as the sections pertaining to the pharmacy bulk package dosage form of the listed drug labeling, with the exception that reference to Lilly Kefzol® (Sterile Cefazolin Sodium) Pharmacy Bulk Vial will be replaced with “Sterile Cefazolin Sodium, USP 100 g and 300 g Pharmacy Bulk Package” and references to other dosage forms will be eliminated. A copy of the draft proposed package insert is provided in attachment C.

The proposed dosage strengths are designed to be used by hospital pharmacies, or centralized compounding pharmacies that provide hospitals organized into networks, with a standard platform of prepared formulation reconstituted in the required strength and filled into syringes for intravenous delivery of medication. The benefit of these dosage strengths is the optimization of drug therapy and delivery of hospital pharmacy services. The new dosage strengths enhance aseptic control since product reconstitution takes place within a closed system design and disposable components are used. Reduced handling of the product with one single bag equivalent to 5 or 15 vials of the reference drug, further ensures that sterility of the product, is maintained during reconstitution and filling into syringes. The proposed bag system configuration is particularly well adapted for use in the hospital or compounding pharmacy.

Thus the use of the 100 g and 300 g Pharmacy Bulk Packages of Sterile Cefazolin Sodium, USP, in the double plastic and foil bag containers, will not only increase efficiency at the hospital or compounding pharmacy level, but will also permit minimal handling of the product that will result in improved quality assurance.

The introduction of the double bag container will not impact on the established safety and efficacy of Sterile Cefazolin Sodium, USP and since the product is an injectable preparation to be administered at the same strength as the reference drug, a bioequivalence study is not viewed as a requirement.

C. Environmental Impact

An environmental impact analysis report is not required for this petition per 21 CFR 25.24.

D. Economic Impact

This information will be provided upon request from the Agency.

E. Certification

The undersigned certifies that, to the best knowledge of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Should you have any questions concerning the foregoing, please contact Eliane Quinn at (602) 944-8002.

Sincerely,

Quinn Consulting Services,

Eliane K. Quinn, M.S.

enc,

EXHIBIT A

Electronic Orange Book Page Showing
the Listing of the Reference
Listed Drug : Eli Lilly and Company's Kefzol®

Electronic Orange Book

Approved Drug Products

with
Therapeutic Equivalence Evaluations

Current through August 1999

Preface

Search by Active Ingredient Search by Applicant Holder

Search by Proprietary Name Search by Application Number

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Orange Book Specific questions email: DRUGPRODUCTS@CDER.FDA.GOV
General drug questions email: DRUGINFO@CDER.FDA.GOV

U.S Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Information Technology
Division of Data Management and Services

Updated: October 26, 1999

Active Ingredient Search Results from "Rx" table for query on "Cefazolin."

	TE Code	RLD					
064170	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	CEFAZOLIN SODIUM	AM PHARM PARTNERS
064169	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1MG BASE/VIAL	CEFAZOLIN SODIUM	AM PHARM PARTNERS
064170	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 20GM BASE/VIAL	CEFAZOLIN SODIUM	AM PHARM PARTNERS
064169	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	CEFAZOLIN SODIUM	AM PHARM PARTNERS
062831	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	CEFAZOLIN SODIUM	APOTHECON
062831	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	CEFAZOLIN SODIUM	APOTHECON
062831	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	CEFAZOLIN SODIUM	APOTHECON
063002		Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10MG BASE/ML	ANCEF IN PLASTIC CONTAINER	BAXTER HLTHCARE
063002		Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 20MG BASE/ML	ANCEF IN PLASTIC CONTAINER	BAXTER HLTHCARE
063209	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	CEFAZOLIN SODIUM	HANFORD GC
063207	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	CEFAZOLIN SODIUM	HANFORD GC
063208	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	CEFAZOLIN SODIUM	HANFORD GC
063214	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	CEFAZOLIN SODIUM	HANFORD GC
063216	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	CEFAZOLIN SODIUM	HANFORD GC
061773	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	KEFZOL	LILLY
061773	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	KEFZOL	LILLY
062557	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	KEFZOL	LILLY
→ 061773	AP	Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 20GM BASE/VIAL	KEFZOL	LILLY
061773	AP	Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 250MG BASE/VIAL	KEFZOL	LILLY
061773	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	KEFZOL	LILLY
062557	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	KEFZOL	LILLY
062989	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	CEFAZOLIN SODIUM	MARSAM
062988	AP	No	CEFAZOLIN	Injectable;	EQ 1GM	CEFAZOLIN	MARSAM

			SODIUM	Injection	BASE/VIAL	SODIUM	
062989	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 20GM BASE/VIAL	CEFAZOLIN SODIUM	MARSAM
062988	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 250MG BASE/VIAL	CEFAZOLIN SODIUM	MARSAM
062988	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	CEFAZOLIN SODIUM	MARSAM
062989	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 5GM BASE/VIAL	CEFAZOLIN SODIUM	MARSAM
050461	AP	Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	ANCEF	SMITHKLINE BEECHAM
050461	AP	Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	ANCEF	SMITHKLINE BEECHAM
064033	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	CEFAZOLIN SODIUM	SMITHKLINE BEECHAM
050461	AP	Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	ANCEF	SMITHKLINE BEECHAM
050461	AP	Yes	CEFAZOLIN SODIUM	Injectable; Injection	EQ 5GM BASE/VIAL	ANCEF	SMITHKLINE BEECHAM
063018	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 10GM BASE/VIAL	CEFAZOLIN SODIUM	TEVA
063016	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 1GM BASE/VIAL	CEFAZOLIN SODIUM	TEVA
063016	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 250MG BASE/VIAL	CEFAZOLIN SODIUM	TEVA
063016	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 500MG BASE/VIAL	CEFAZOLIN SODIUM	TEVA
063018	AP	No	CEFAZOLIN SODIUM	Injectable; Injection	EQ 5GM BASE/VIAL	CEFAZOLIN SODIUM	TEVA

Thank you for searching the Electronic Orange Book

Return to Electronic Orange Book Home Page

EXHIBIT B

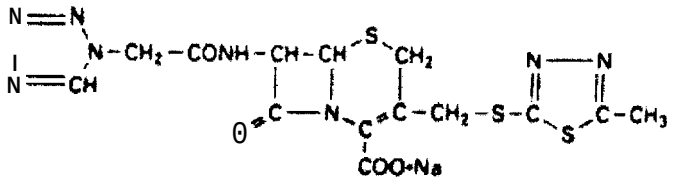
Copy of the Package Insert for
the Reference Listed Drug
Eli Lilly and Company's Kefzol®

PDR® entry for
Kefzol Vials, ADD-Vantage (ELI LILLY AND COMPANY)

DESCRIPTION

Kefzol® (cefazolin for injection, USP) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of
3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1 H
-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct- 2-ene-2-caboxylic acid.

Structural Formula:



The sodium content is 46 mg per gram of cefazolin.

Kefzol in lyophilized form is supplied in vials equivalent to 500 mg or 1 gram of cefazolin: in "Piggyback" Vials for intravenous admixture equivalent to 1 gram of cefazolin; and in Pharmacy Bulk Vials equivalent to 10 grams of cefazolin.

CLINICAL PHARMACOLOGY

Human Pharmacology: After intramuscular administration of Kefzol to normal volunteers, the mean serum concentrations were 37 mcg/mL at one hour and 3 mcg/mL at eight hours following a 500 mg dose, and 64 mcg/mL at one hour and 7 mcg/mL at eight hours following a 1 gram dose.

Studies have shown that the following intravenous administration of Kefzol to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at eight hours for a 1 gram dose. . . . , .

The serum half-life for Kefzol is approximately 1.8 hours following I.V. administration and approximately 2.0 hours following I.M. administration.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for one hour (approximately 250 mg) and 1.5 mg/kg the next two hours (approximately 100 mg). Kefzol produced a steady serum level at the third hour of approximately 28 mcg/mL.

Studies in patients hospitalized with infections indicated that Kefzol (cefazolin for injection) produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to five times; however, in patients with obstructive biliary disease, bile levels of Kefzol are considerably lower than serum levels (< 1.0 mcg/mL).

In synovial fluid, the Kefzol level becomes comparable to that reached in serum at about four hours after drug administration.

Studies of cord blood show prompt transfer of Kefzol across the placenta. Kefzol is present in very low concentrations in the milk of nursing mothers.

Kefzol is excreted unchanged in the urine. In the first six hours approximately 60% of the drug is excreted in the urine and this increases to 70%-80% within 24 hours. Kefzol achieves peak urine concentrations of approximately 2400 mcg/mL and 4000 mcg/mL respectively following 500 mg and 1 gram intramuscular doses.

In patients undergoing peritoneal dialysis (2 L/hr.), Kefzol produced mean serum levels of approximately 10 and 30 mcg/mL after 24 hours' instillation of a dialyzing solution containing 50 mg/L and 150 mg/L, respectively. Mean peak levels were 29 mcg/mL (range 13-44 mcg/mL) with 50 mg/L (three patients), and 72 mcg/mL (range 26-142 mcg/mL) with 150 mg/L (six patients). Intraperitoneal administration of Kefzol is usually well tolerated.

Controlled studies on adult normal volunteers, receiving I gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline, phosphatase, BUN, creatinine and urinalysis, indicated no clinically significant changes attributed to Kefzol.

Microbiology: *In* vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Kefzol (cefazolin for injection) is active against the following organisms *in* vitro and in clinical infections:

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus epidermidis

Methicillin-resistant staphylococci are uniformly resistant to cefazolin

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae	*Enterobacter aerogenes*
Escherichia coli	*Haemophilus influenzae*
Proteus mirabilis	
Klebsiella species	

Most strains of indole-positive *Proteus (Proteus vulgaris), Enterobacter cloacae, Morganella morganii* and *Providencia reffgeri* are resistant.

Serratia, Pseudomonas, Mima, Herellea species are almost uniformly resistant to cefazolin.

Disk Susceptibility Tests

Disk diffusion technique --Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure 1 has been recommended for use with disks to test susceptibility to cefazolin.

Reports from a laboratory using the standardized single-disk susceptibility test 1 with a 30 mcg

cefazolin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones 15 to 17 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

For gram-positive isolates, a zone of 18 mm is indicative of a cefazolin-susceptible organism when tested with either the cephalosporin-class disk (30 mcg cephalothin) or the cefazolin disk (30 mcg cefazolin).

Gram-negative organisms should be tested with the cefazolin disk (using the above criteria), since cefazolin has been shown by *in* vitro tests to have activity against certain strains of Enterobacteriaceae found resistant when tested with the cephalothin disk Gram-negative organisms having zones of less than 18 mm around the cephalothin disk may be susceptible to cefazolin.

Standardized procedures require use of control organisms. The 30 mcg cefazolin disk should give zone diameter between 23 and 29 mm for *E. coli* ATCC 25922 and between 29 and 35 mm for *S. aureus* ATCC 25923.

The cefazolin disk should not be used for testing susceptibility to other cephalosporins

Dilution Techniques -A bacterial isolate may be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 mcg per mL. Organisms are considered resistant if the MIC is equal to or greater than 64 mcg per mL.

The range of MIC's for the control strains are as follows:

S. aureus ATCC 25923, 0.25-1.0 mcg/mL

E. coli ATCC 25922, 1.0-4.0 mcg/mL

1 Bauer, AW.; Kirby, W.M.M.; Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am J. Clin, Path. 45:493, 1966. Standardized Disc Susceptibility Test, Federal Register 39:19182-19184, 1974.
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INDICATIONS AND USAGE

Kefzol (cefazolin for injection) is indicated in the treatment of the following serious infections due to susceptible organisms:

RESPIRATORY TRACT INFECTIONS due to *Streptococcus pneumoniae, Klebsiella* species *Haemophilus injluenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Kefzol is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of Kefzol in the subsequent prevention of rheumatic fever are not available

at present.

URINARY TRACT INFECTIONS due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

SKIN *AND* SKIN STRUCTURE INFECTIONS due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta hemolytic streptococci and *other strains* of streptococci.

BILIARY TRACT INFECTIONS due to *Escherichia coli , various strains* of streptococci *Proteus mirabi lis, Klebsiella* species and *Staphylococcus aureus.*

BONE *AND* JOINT INFECTIONS due to *Staphylococcus aureus.*

GENITAL INFECTIONS (i.e., prostatitis epididymitis) *due* to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterococci.

SEPTICEMIA due to *Streptococcus neumoniae, Staphylococcus aureus* (penicillin sensitive and penicillin-resistant). *Proteus mirabilis, Escherichia coli* and *Klebsiella* species.

ENDOCARDITIS due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptible studies should be performed to determine susceptibility of the causative organism to Kefzol .

PERIOPERATIVE PROPHYLAXIS: The prophylactic administration of Kefzol preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those over 70 year of age, with acute cholecystitis, obstructive jaundice or common duct bile stones).

The perioperative use of Kefzol may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of Kefzol should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Kefiol may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted

(See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

KEFZOL (CEFAZOLIN FOR INJECTION) IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN

HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS, THERE HAVE BEEN REPORTS OF INDIVJDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS, BEFORE INITIATING THERAPY WITH KEFZOL . CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, KEFZOL SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY SHOULD BE INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRJNE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Kefiol , and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mid cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against C. *difficile* colitis.

PRECAUTIONS

General -Prolonged use of Kefzol (cefazolin for injection) may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When Kefzol is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see DOSAGE AND ADMINISTRATION).

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Kefzol , as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Interactions --Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Drug/Laboratory Test Interactions --A false positive reaction for glucose in the urine may occur with Benedict's solution. Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape@.

Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

Carcinogenesis/Mutagenesis --Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Kefzol (cefazolin for injection) have not been performed

Pregnancy --Tcratogenic Effects--Pregnancy Category B. Reproduction studies have been performed in rats, mice and rabbits at doses up to 25 times the human dose and have revealed no

evidence of impaired fertility or harm to the fetus due to Kefzol . There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery -When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

Nursing Mothers -- Kefzol is present in very low concentrations in the milk of nursing mothers Caution should be exercised when Kefzol (cefazolin for injection) is administered to a nursing woman.

Pediatric Use -Safety and effectiveness for use in prematures and infants under one month of age have not been established See DOSAGE AND ADMINISTRATION for recommended dosage in children over one month.

ADVERSE REACTIONS

The following reactions have been reported:
Gastrointestinal : Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Nausea and vomiting have been reported rarely.
Allergic : Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.
Hematologic : Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.
Hepatic and Renal : Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.
Local Reactions : Rare instances of phlebitis have been reported at site of injection. Pain at the site of injection after intramuscular administration has occurred infrequently. Some induration has occurred.
Other Reactions : Genital and anal pruritus (including vulvar pruritus, genital moniliasis and vaginitis).

DOSAGE AND ADMINISTRATION

Usual Adult Dosage

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hrs.
Mild infections caused by susceptible gram+cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia) *	1 gram to 1.5 grams	every 6 hours

*In rare instances, doses up to 12 grams of Kefzol per day have been used.

Perioperative Prophylactic Use

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

1. 1 gram I.V. or I.M. administered 1/2 hour to 1 hour prior to the start of surgery.
2. For lengthy operative procedures (e.g., 2 hours or longer), 500 mg to 1 gram I.V. or I.M. during surgery (administration modified &pending on the duration of the operative procedure).
3. 500 mg to 1 gram I.V. or I.M. every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 hour to 1 hour) prior to the start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of the initial surgical incision; and (2) Kefzol be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Kefzol (cefazolin for injection) may be continued for 3 to 5 days following the completion of surgery.

Dosage Adjustment for Patients With Reduced Renal Function

Kefzol may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 mL/min, or greater or a serum creatinine of 1.5 mg % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 mL/min, or serum creatinine of 1.6 to 3.0 mg % can also be given full doses but dosage should be restricted to at least 8 hour intervals. Patients with creatinine clearance rates of 11 to 34 mL/min, or serum creatinine of 3.1 to 4.5 mg % should be given 1/2 the usual dose every 12 hours, Patients with creatinine clearance rates of 10 mL/min, or less or serum creatinine of 4.6 mg % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. Patients undergoing peritoneal dialysis: see Human Pharmacology.

Pediatric Dosage

In children, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and infants under one month has not been established, the use of Kefzol (cefazolin for injection) in these patients is not recommended.

Pediatric Dosage Guide

Weight		15 mg/kg/Day Divided into 3 Doses		25mg/kg/Day Divided into 4 Doses	
Lbs	Kg	Approximate Single Dose mg/Q8^	Vol. (mL) needed with dilution of125	Approximate Single Dose mg/q6h	Vbl.(mL) needed with dilution of 125 mg/mL
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9.0	75mg	0.60 mL	55 mg	0.45 mL
30	13.6	115mg	0.90 mL	85 mg	0.70 mL
40	18.1	150 mg	1.20 mL	115mg	0.90 mL
50	22.7	190mg	1.50 mL	14Omg	1.10 mL

Weight			50 mg/kg/Day Divided into 3 Doses		50 mg/kg/Day Divided into 4 Doses	
Lbs	K	g	Approximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 225	Approximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 225 mg/mL
10	4.5		75 mg	0.35 mL	55 mg	0.25 mL
20	9.0		150 mg	070 mL	llOmg	0.50 mL
30	13.6		225 mg	1.00 mL	170 mg	0.75 mL
40	18.1		300 mg	1.35 mL	225 mg	1.00 mL
50	22.7		375 mg	1.70 mL	285 mg	1.25 mL

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min.), 60% of the normal daily dose given in equally divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/min.), 25% of the normal daily dose given in equally divided doses every 12 hours should be adequate. Children with severe renal impairment (creatinine clearance of 20 to 5 mL/min.) may be given 10% of the normal daily dose every 24 hours. All dosage recommendations apply after an initial loading dose.

RECONSTITUTION

Preparation of Parenteral Solution

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration, If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

When reconstituted or diluted according to the instructions below, Kefzol (cefazolin for injection) is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F). Reconstituted solutions may range in color from pale yellow to yellow without a change in potency.

Single-Dose Vials

For I.M. injection, I.V. direct (bolus) injection or I.V. infusion, reconstitute with Sterile Water for Injection according to the following table. SHAKE WELL.

Vial Size	'Amount of Diluent	Approximate Concentration	Approximate Available Volume
500 mg	2.0 mL	225mg/mL	2.2 mL
1 gram	2.5 mL	330 mg/mL	3.0 mL

Pharmacy Bulk Vials

Add Sterile Water for Injection, Bacteriostatic Water for Injection or Sodium Chloride Injection according to the table below. SHAKE WELL.

Vial Size	Amount of Diiuent	Approximate Concentration	Approximate Available Volume
10 grams	45 mL	1 gram/5 mL	51 mL
	96 mL	1 gram/IO mL	102 mL

“Piggyback” Vials

Reconstitute with 50 to 100 mL of Sodium Chloride Injection or other I.V. solution listed under ADMINISTRATION. When adding diluent to vial, allow air to escape by using a small vent needle or by pumping the syringe. SHAKE! WELL. Administer with primary I.V. fluids, as a single dose.

ADMINISTRATION

Intramuscular Administration-- Reconstitute vials with Sterile Water for Injection according to the dilution table above. Shake well until dissolved. Kefzol should be injected into a large muscle mass. Pain on injection is infrequent in Kefiol .

Intravenous Administration-- Direct (bolus) injection: Following reconstitution according to the above table, further dilute vials with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion. Dilute reconstituted Kefiol in 50 to 100 mL of one of the following solutions:

Sodium Chloride Injection, USP

5% or 10% Dextrose Injection, USP

5% Dextrose in Lactated Ringer’s Injection, USP

5% Dextrose and 0.9% Sodium Chloride Injection, USP

5% Dextrose and 0.45% Sodium Chloride Injection, USP

5% Dextrose and 0.2% Sodium Chloride Injection, USP

Lactated Ringer’s Injection, USP

Invert Sugar 5% or 10% in Sterile Water for Injection

Ringer’s Injection, USP

5% Sodium Bicarbonate Injection, USP

HOW SUPPLIED

Kefzol (cefazolin for injection)-supplied in vials equivalent to 500 mg or 1 gram of cefazolin in "Piggyback" Vials for intravenous admixture equivalent *to* 1 gram of cefazolin; and in Pharmacy Bulk vials equivalent to 10 grams of cefazolin.

Vials:

500 mg, 10-mL size (No. 767)--(Traypak * of 25) NDC 0002-1497-25

1 gram 10-mL size (No. 768)--(Traypak of 25) NDC 0002-1498-25

1 gram, 100-mL size (No. 701 1)**/* --(Traypak of 10) NDC 0002-701 l-10

Pharmacy Bulk Vials:

10 gram, 100-mL size (No. 7014)--(Traypak of 6) NDC 0002-7014-16

Also Available:

Faspak **/** :

1 gram (No. 7202) **/* --(Faspak of 96) NDC 0002-7202-74

ADD-Vantage§ Vials:

500 mg (No. 7265)--(Traypak of 25) NDC 0002-7265-25

1 gram (No. 7266)--(Traypak of 25) NDC 0002-7266-25

The above ADD-Vantage Vials are to be used only with Abbott Laboratories' 50-mL or 100-mL Flexible Diluent Containers containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection.

Instructions for use of the ADD-Vantage Vials are enclosed in the package.

*Traypak™ (multivial§ADD-Vantage® carton. Lilly)

.(vials and diluent **/* For IV usecontainers, Abbott)

. **/** Faspak® (flexible plastic bag. Lilly)

As with other cephalosporins, Kefzol tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

Before reconstitution protect from light and store between 15° and 30°C (59" and 86°F)

CAUTION --Federal (USA) law prohibits dispensing without prescription.

Literature revised November 1997.

Manufactured for

ELI LILLY AND COMPANY

Indianapolis, IN 46285, USA

by

BMH Limited

Philadelphia, PA 19 10 1

EXHIBIT C

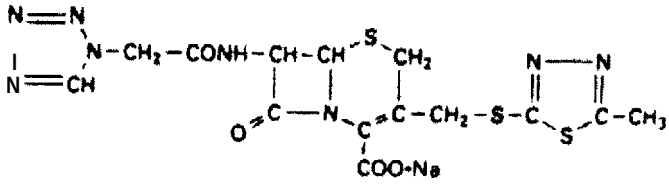
Copy of the Proposed Draft Package Insert for
Sterile Cefazolin Sodium, USP

STERILE CEFAZOLIN SODIUM, USP

DESCRIPTION

Sterile Cefazolin Sodium, USP is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl}-8-oxo-7-[2-(1 H -tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct- 2-ene-2-caboxylic acid.

Structural Formula:



The sodium content is 46 mg per gram of cefazolin.

Sterile Cefazolin Sodium, USP in lyophilized form is supplied in Pharmacy Bulk Packages consisting of double bags, an inner plastic bag and an outer foil wrap containing the equivalent to 100g or 300 g of cefazolin:

CLINICAL PHARMACOLOGY

Human Pharmacology: After intramuscular administration of Sterile Cefazolin Sodium, USP to normal volunteers, the mean serum concentrations were 37 mcg/mL at one hour and 3 mcg/mL at eight hours following a 500 mg dose, and 64 mcg/mL at one hour and 7 mcg/mL at eight hours following a 1 gram dose.

Studies have shown that the following intravenous administration of Sterile Cefazolin Sodium, USP to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at eight hours for a 1 gram dose.

The serum half-life for Sterile Cefazolin Sodium USP is approximately 1.8 hours following I.V. dministration and approximately 2.0 hours following I.M. administration.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for one hour (approximately 250 mg) and 1.5 mg/kg the next two hours (approximately 100 mg). Sterile Cefazolin Sodium, USP produced a steady serum level at the third-hour of approximately 28 mcg/mL.

Studies in patients hospitalized with infections indicated that Sterile Cefazolin Sodium, USP produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to five times; however, in patients with obstructive biliary disease, bile levels of Sterile Cefazolin Sodium, USP are considerably lower than serum levels (cl.0 mcg/mL).

In synovial fluid the Sterile Cefazolin Sodium, USP level becomes comparable to that reached in serum at about four hours after drug administration.

Studies of cord blood show prompt transfer of Sterile Cefazolin Sodium, USP across the placenta. Sterile Cefazolin Sodium, USP is present in very low concentrations in the milk of nursing mothers.

Sterile Cefazolin Sodium, USP is excreted unchanged in the urine. In the first six hours approximately 60% of the drug is excreted in the urine and this increases to 70%-80% within 24 hours. Sterile Cefazolin Sodium, USP achieves

peak urine concentrations of approximately 2400 mcg/mL and 4000 mcg/mL respectively following 500 *mg* and 1 gram intramuscular doses.

In patients undergoing peritoneal dialysis (2 L/hr.), Sterile Cefazolin Sodium, USP produced *mean* serum levels of approximately 10 and, 30 mcg/mL after 24 hours' instillation of a dialyzing solution containing 50mg/L and 150 mg/L, respectively. Mean peak levels were 29 mcg/mL (range 13-44 mcg/mL) with 50mg/L (three patients), and 72 mcg/mL (range 26-142 mcg/mL) with 150 mg/L (six patients).
Intraperitoneal administration of Sterile Cefazolin Sodium, USP is usually well tolerated.

Controlled studies *on* adult normal volunteers, receiving 1 gram 4 *times a day* for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline, phosphatase, BUN, creatinine and urinalysis, indicated no clinically significant changes attributed to Sterile Cefazolin Sodium, USP.

Microbiology: In *vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. Sterile Cefazolin Sodium, USP is active against the following organisms *in vitro* and in clinical infections:

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus epidermidis

Methicillin-resistant staphylococci are uniformly resistant to cefazolin

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae	*Enterobacter aerogenes*
Escherichia coli	*Haemophilus influenzae*
Proteus mirabilis	
Klebsiella species	

Most strains of indole-positive Proteus *(proteus vulgaris), Enterobacter cloacae, Morganella morganii* and *Providencia rettgeri* are resistant.

Serratia, Pseudomonas, Mima, Herellea species are almost uniformly resistant to cefazolin.

Disk Susceptibility Tests
Disk diffusion technique --Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure 1 has been recommended for use with disks to test susceptibility to cefazolin.

Reports from a laboratory using the standardized singledisk susceptibility test 1 with a 30 mcg cefazolin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones 15 to 17 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

For gram-positive isolates, a zone of 18 mm is indicative of a cefazolin-susceptible organism when tested with either the cephalosporin-class disk (30 mcg cephalothin) or the cefazolin disk (30 mcg cefazolin).

Gram-negative organisms should be tested with the cefazolin disk (using the above criteria), since cefazolin has been shown by *in vitro* tests to have activity against certain strains of Enterobacteriaceae found resistant when tested with the cephalothin disk. Gram-negative organisms having zones of less than 18 mm around the cephalothin disk may be susceptible to cefazolin.

Standardized procedures require use of control organisms. The 30 mcg cefazolin disk should give zone diameter between 23 and 29 mm for *E. coli* ATCC 25922 and between 29 and 35 mm for *S. aureus* ATCC 25923.

The cefazolin disk should not be used for testing susceptibility to other cephalosporins

Dilution Techniques -A bacterial isolate may be considered susceptible if the minimal inhibitory concentration (MIC) for cefazolin is not more than 16 mcg per mL. Organisms are considered resistant if the MIC is equal to or greater than 64 mcg per mL.

The range of MIC's for the control strains are as follows:

S. aureus ATCC 25923, 0.25-1.0 mcg/mL

E. coli ATCC 25922, 1.0-4.0 mcg/mL

1 Bauer, AW.; Kirby, W.M.M.; Sherris, J.C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am J. Clin. Path 45:493, 1966. Standardized Disc Susceptibility Test, Federal Register 39:19182-19184, 1974.

INDICATIONS AND USAGE

Sterile Cefazolin Sodium, USP is indicated in the treatment of the following serious infections due to susceptible organisms:

RESPIRATORY TRACT INFECTIONS *due* to *Streptococcus pneumoniae, Klebsiella* species *Haemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Sterile Cefazohn Sodium, USP is effective in the eradication of streptococci from the nasopharynx, however, data establishing the efficacy of Sterile Cefazolin Sodium, USP in the subsequent prevention of rheumatic fever are not available at present.

URINARY TRACT INFECTIONS *due* to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterobacter and enterococci.

SKIN AND SKIN STRUCTURE INFECTIONS *due* to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), group A beta hemolytic streptococci and other strains of streptococci.

BILIARY TRACT *INFECTIONS* due to *Escherichia coli , various* strains of streptococci *Proteus mirabifis, Klebsiella* species and *Staphylococcus aureus.*

BONE *AND* JOINT INFECTIONS due to *Staphylococcus aureus.*

GENITAL INFECTIONS (i.e., prostatitis epididymitis) due to *Escherichia coli, Proteus mirabilis, Klebsiella* species and some strains of enterococci.

SEPTICEMIA due to *Streptococcus neumoniae, Staphylococcus aureus* (penicillin sensitive and penicillin-resistant). *Proteus mirabilis, Eschen'chia coli* and *Klebsiella species.*

ENDOCARDITIS due to *Staphylococcus aureus (penicillin-sensitive* and penicillin-resistant) and group A beta-hemolytic streptococci.

Appropriate culture and susceptible studies should be performed to determine susceptibility of the causative organism to Sterile Cefazolin Sodium, USP .

PERIOPERATIVE PROPHYLAXIS: The prophylactic administration of Sterile Cefazolin Sodium, USP preoperatively, intraoperatively and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those over 70 year of age, with acute cholecystitis, obstructive jaundice or common duct bile stones).

The perioperative use of Sterile Cefazolin Sodium USP may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of Sterile Cefazolin Sodium, USP should usually be discontinued within a 24-hour period after the surgical procedure, In surgery where the occurrence of infection may be particularly devastating (e.g., open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Sterile Cefazolin Sodium, USP may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted. (See DOSAGE AND ADMINISTRATION.)

CONTRAINDICATIONS

STERILE CEFAZOLIN SODIUM, USP IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS, BEFORE INITIATING THERAPY WITH STERILE CEFAZOLIN SODIUM, USP . CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, STERILE CEFAZOLIN SODIUM, USP SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY SHOULD BE INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Sterile Cefazolin Sodium, USP , and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic *measures* should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone.
In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General --Prolonged use of Sterile Cefazolin Sodium, USP may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential

When Sterile Cefazolin Sodium, USP is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see DOSAGE AND ADMINISTRATION).

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

Sterile Cefazolin Sodium, USP , as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug Interactions --Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Drug/Laboratory Test Interactions -A false positive reaction for glucose in the urine may occur with Benedict's solution. Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape@.

Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

Carcinogenesis/Mutagenesis --Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of Sterile Cefazolin Sodium, USP have not been performed.

Pregnancy --Teratogenic Effects--Pregnancy Category B. Reproduction studies have been performed in rats, mice and rabbits at doses up to 25 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Sterile Cefazolin Sodium, USP . There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery --When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

Nursing Mothers -- Sterile Cefazolin Sodium, USP is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when Sterile Cefazolin Sodium, USP is administered to a nursing woman.

Pediatric Use --Safety and effectiveness for use in prematures and infants under one month of age have not been established. See DOSAGE AND ADMINISTRATION for recommended dosage in children over one month.

ADVERSE REACTIONS

The following reactions have been reported:
Gastrointestinal : Diarrhea, oral candidiasis (oral thrush), vomiting nausea, stomach cramps, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS). Nausea and vomiting have been reported rarely.
Allergic : Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.
Hematologic : Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic and Renal : Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.
Local Reactions : Rare instances of phlebitis have been reported at site of injection. Pain at the site of injection after intramuscular administration has occurred infrequently. Some induration has occurred.
Other Reactions : Genital and anal pruritus (including vulvar pruritus, genital moniliasis and vaginitis).

DOSAGE AND ADMINISTRATION

Usual Adult Dosage

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hrs.
Mild infections caused by susceptible gram + cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia) *	1 gram to 1.5 grams	every 6 hours

*In ram instances, doses up to 12 grams of Sterile Cefazolin Sodium, USP per day have been used.

Perioperative Prophylactic Use

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

1.1 gram I.V. or I.M. administered 1/2 hour to 1 hour prior to the start of surgery.
2.For lengthy operative procedures (e.g., 2 hours or longer), 500 mg to 1 gram I.V. or I.M. during surgery (administration modified depending on the duration of the operative procedure). 3.500 mg to 1 gram I.V. or I.M. every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (1/2 hour to 1 hour) prior to the start of surgery so that adequate antibiotic levels are present in the serum 'and tissues at the time of the initial surgical incision; and (2) Sterile Cefazolin Sodium, USP be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (e.g. , open-heart surgery and prosthetic arthroplasty), the prophylactic administration of Sterile Cefazolin Sodium, USP may be continued for 3 to 5 days following the completion of surgery.

Dosage Adjustment for Patients With Reduced Renal Function

Sterile Cefazolin Sodium, USP may be used in patients with reduced renal function with the following dosage adjustments:
Patients with a creatinine clearance of 55 mL/min, or greater or a serum creatinine of 1.5 mg % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 mL/min, or serum creatinine of 1.6 to 3.0 mg % can also be given full doses but dosage should be restricted to at least 8 hour intervals. Patients with creatinine clearance rates of 11 to 34 mL/min, or serum creatinine of 3.1 to 4.5 mg % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 mL/min, or less or serum creatinine of 4.6 mg % or greater should be

given ½ the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. Patients undergoing peritoneal dialysis: see Human Pharmacology

Pediatric Dosage

In children, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and infants under one month has not been established, the use of Sterile Cefazolin Sodium, USP in these patients is not recommended.

Pediatric Dosage Guide

Weight		/S mg/kg/Day Divided into 3 Doses		25mg/kg/Day Divided into 4 Doses	
Lbs	K g	Approximate Single Dose mg/Q8^	Vd. (mL) needed with dilution of 125	Approximate Single Dose mg/q6h	Vbl.(mL) needed with dilution of 125 mg/mL
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9.0	75 mg	0.60 mL	55 mg	0.45 mL
30	13.6	115 mg	0.90 mL	85mg	0.70 mL
40	18.1	150 mg	1.20 mL	115mg	0.90 mL
50	22.7	190 mg	1.50 mL	140 mg	1.10 mL

Weight		50 mg/kg/Day Divided into 3 Doses		50 mg/kg/Day Divided into 4 Doses	
Lbs	Kg	Approximate Single Dose mg/q8h	Vol. (mL) needed with dilution of 225	Approximate Single Dose mg/q6h	Vol. (mL) needed with dilution of 225 mg/mL
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9.0	150 mg	070 mL	IIOmg	0.50 mL
30	13.6	225 mg	1.00 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1.00 mL
50	22.7	375 mg	1.70 mL	285 mg	1.25 mL

In children with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min.), 60% of the normal daily dose given in equally divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/min.), 25% of the normal daily dose given in equally divided doses every 12 hours should be adequate. Children with severe renal impairment (creatinine clearance of 20 to 5 mL/min.) may be given 10% of the normal daily dose every 24 hours. All dosage recommendations apply after an initial loading dose.

RECONSTITUTION

Preparation of Parenteral Solution

Parenteral drug products should be SHAKEN WELL when reconstituted, and inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the dtug solution should be discarded.

When reconstituted or diluted according to the instructions below, Sterile Cefazolin Sodium, USP is stable for 24 hours at room temperature or for 10 days if stored under refrigeration (5°C or 41°F).

Reconstituted solutions may range in color from pale yellow to yellow without a change in potency

Pharmacy Bulk Vials

Add Sterile Water for Injection,
according to the table below. SHAKE WELL.

Vial Size	Amount of Diluent	Approximate Concentration	Approximate Available Volume
100 grams	960 mL	1 gram/10 mL	1020 mL
300 grams	2880 mL	1 gram/10 mL	3060 mL

ADMINISTRATION

Intravenous Administration-- Direct (bolus) injection: Following reconstitution according to the above table, further dilute with approximately 5 mL Sterile Water for Injection. Inject the solution slowly over 3 to 5 minutes, directly or through tubing for patients receiving parenteral fluids (see list below).

Intermittent or continuous infusion. Dilute reconstituted Sterile Cefazolin Sodium, USP in 50 to 100 mL of one of the following solutions:

Sodium Chloride Injection, USP

5% or 10% Dextrose Injection, USP

5% Dextrose in Lactated Ringer's Injection, USP

5% Dextrose and 0.9% Sodium Chloride Injection, USP

5% Dextrose and 0.45% Sodium Chloride Injection, USP

5% Dextrose and 0.2% Sodium Chloride Injection, USP

Lactated Ringer's Injection, USP

Invert Sugar 5% or 10% in Sterile Water for Injection

Ringer's Injection, USP

5% Sodium Bicarbonate Injection, USP

HOW SUPPLIED

Sterile Cefazolin Sodium, USP --supplied in Pharmacy
Bulk Packages bags equivalent to 100 grams and 300 grams of cefazolin.

Pharmacy Bulk Packages in double plastic bags (foil outer wrap):

100 grams, NDC _____
300 grams, NDC_____.

As with other cephalosporins, Sterile Cefazolin Sodium, USP tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

Before reconstitution protect from light and store between 15" and 30°C (59° and 86°F)

CAUTION --Federal (USA) law prohibits dispensing without prescription.

Literature revised November 1999.

Manufactured for

inn
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00034969-51

RETURN RECEIPT
REQUESTED

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857